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The Association of ^{18}F-FDG-PET/CT Parameters with Survival in Malignant Pleural Mesothelioma

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ABSTRACT

Purpose: Malignant pleural mesothelioma (MPM) is a disease with poor prognosis despite multimodal therapy but there is variation in survival between patients. Prognostic information is therefore potentially valuable in managing patients, particularly in the context of clinical trials where patients could be stratified according to risk. Therefore we have evaluated the prognostic ability of parameters derived from baseline 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT).

Methods**:** In order to determine the relationships between metabolic activity and prognosis we reviewed all ^{18}F-FDG PET/CT scans used for pre-treatment staging of MPM patients in our institution between January 2005 and December 2011 (n = 60) and measured standardized uptake values (SUV) including mean, maximum and peak values, metabolic tumour volume (MTV) and total lesion glycolysis (TLG). Overall survival (OS) or time to last censor was recorded, as well as histological subtypes.

Results**:** Median follow up was 12.7 months (1.9 - 60.9) and median OS was 14.1 months (1.9 - 54.9). By univariable analysis histological subtype (p = 0.013), TLG (p = 0.024) and MTV (p = 0.038) were significantly associated with OS and SUVmax was borderline (p = 0.051). On multivariable analysis histological subtype and TLG were associated with OS but at borderline statistical significance (p = 0.060 and 0.058, respectively). No statistically significant differences in any PET parameters were found between the epithelioid and non-epithelioid histological subtypes.

Conclusion: ^{18}F-FDG PET/CT parameters that take into account functional volume (MTV, TLG) show significant associations with survival in patients with MPM before adjusting for histological subtype and are worthy of further evaluation to determine their ability to stratify patients in clinical trials.

Key words: mesothelioma, ^{18}F-FDG PET/CT, prognosis, standardised uptake value, total lesion glycolysis, metabolic tumour volume

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a primary tumour of the pleura that is causally linked to asbestos exposure in most cases. The disease arises in the parietal pleura, spreads contiguously to invade local structures, and can pass through the diaphragm into the abdominal cavity. The incidence of MPM is increasing, with the UK being currently in the midst of a 'mesothelioma epidemic' with the number of deaths having increased from 153 per annum in 1968 to 2046 in 2005 [1]. The disease is associated with poor prognosis and median survival from diagnosis is usually less than a year [2]. There is no known cure for MPM but treatment may involve a combination of radical surgery, chemotherapy and radiotherapy. To date, the outcomes of multi-modality therapy regimens have been disappointing with modest survival benefit [2,3]. Systemic chemotherapy plays a significant role in the management of this disease but is of limited efficacy with universally low objective tumour response rates in the clinic and a failure to impact highly on survival [3]. A therapeutic plateau has therefore been reached with conventional cytotoxic treatment requiring both the introduction of new biologically targeted drugs and, most importantly, a better understanding of the tumour biology which could lead to a better patient selection for targeted or radical therapies.

2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) is the most commonly-used imaging tracer in combined positron emission tomography / computed tomography (PET/CT) [4] and has been widely utilized to stage and diagnose cancer [5]. Mesothelioma studies to date have shown that ^{18}F-FDG PET/CT may differentiate benign from malignant pleural disease, detect mesothelioma recurrence and provide prognostic information in terms of staging, survival and mortality [6-10]. There is therefore potential to use the metabolic information from ^{18}F-

FDG PET/CT to better define the aggressiveness of MPM in individual patients such that treatment could be stratified in clinical trials.

The study hypothesis was that parameters derived from ^{18}F-FDG PET/CT, reflecting tumour metabolic activity, have prognostic significance in MPM. The aim of this retrospective study was to determine whether PET parameters reflecting metabolic activity (including maximum standardized uptake value (SUVmax), mean (SUVmean) and peak (SUVpeak) SUVs) and/or tumour volume (including metabolic tumour volume (MTV) and total lesion glycolysis (TLG)) [11] were associated with overall survival in a large cohort of patients scanned in our institution.

MATERIALS AND METHODS

Subjects

All pre-treatment staging ^{18}F-FDG PET/CT scans performed in patients with MPM at our institution between January 2006 and December 2011 were selected from the institutional PET database. Patients were included if they underwent whole body ^{18}F-FDG PET/CT as part of their routine preoperative staging procedure before any therapy. Any patients with prior pleurodesis were excluded in view of the non-malignant uptake of ^{18}F-FDG that results from this procedure. Demographic and clinicopathological data, including histological subtype, treatment details and overall survival (OS) were collected. Institutional approval was obtained to perform this retrospective analysis and requirement for informed consent was waived.

^{18}F-FDG PET/CT and Analysis

^{18}F-FDG PET-CT scans were acquired using the same routine clinical oncology imaging protocol in the same institution on one of two scanners (Discovery VCT or DST, GE Healthcare, Waukesha, US). All ^{18}F-FDG PET/CT scans were performed at 90 min (mean 89.7 min +/- 9.3) post injection of 350-400 MBq ^{18}F-FDG after a 4 to 6 hour fast. Images were reconstructed using OSEM (2 iterations, 20 subsets) with a reconstructed slice thickness of 3.27mm and pixel size 5mm. The CT component of PET/CT scans was acquired at 140 kVp and 65 mAs without administration of oral or intravenous contrast agent and CT data was used for attenuation correction. All patients' blood glucose levels were < 10 mmol/L at the time of ^{18}F-FDG injection.

^{18}F-FDG PET data was analyzed on a dedicated workstation to measure SUVmax, SUVmean, SUVpeak, MTV (total volume of metabolically active tumour within a defined volume of interest) and TLG (SUVmean x MTV) [11] in primary MPM lesions using semi-automated software for volume of interest (VOI) placement and analysis (Hermes Gold 3, Stockholm) by a single operator. VOIs were initially selected using a predefined threshold of 40% of SUVmax [12] but were adjusted by the operator if non-tumoural areas of activity were incorrectly included within the VOI. Sixteen cases required a reduction in the threshold down to levels as far as 20% of SUVmax and 3 required an increase as far as 60%. Interobserver variability in performing these measurements with similar software has previously been reported as less than 5% [13].

Statistical Analysis

OS was defined as the time in months between the PET scan and the date of death. The time between PET scans and last censor was recorded in surviving patients. In each of the PET parameters, differences between epithelioid and non-epithelioid histological subtypes were tested by the Mann-Whitney U-test excluding the 9 cases with unknown histology. Subgroup analyses were not undertaken in other histological subtypes due to the small number of patients in each group.

Cox regression was used to examine the effects of the PET parameters and other variables upon the survival outcomes and were performed in two stages. Initially the individual association of each variable with survival times was examined in a series of univariable analyses. Subsequently a multivariable analysis was performed to examine the joint effect of the variables retaining only variables significantly associated with survival. Some factors were omitted from the multivariable analyses where collinearity was found, with the clinically more relevant factors retained. Kaplan-Meier curves were generated for factors found to be significant predictors on univariable analysis. Differences in Kaplan-Meier survival curves were evaluated using a non-parametric log-rank test. A cut-point for the level of the PET parameters was calculated maximizing the sum of sensitivity and specificity from receiver operating characteristic (ROC) curves. P-values of less than 0.05 were considered statistically significant.

RESULTS

Sixty patients (mean age = 64.8 years, 51 males) were identified who had baseline ^{18}F-FDG PET/CT scans before treatment (Table 1). Thirty one patients had epithelioid subtype, with the remaining patients showing a mixed (n = 13), sarcomatoid (n = 5) or desmoplastic (n = 2)

subtype. In 9 patients it was not possible to confirm histological results. TNM and overall stage were assessed by a combination of surgery, when performed, diagnostic CT scans and ^{18}FDG PET/CT (Table 1). Thirty-two patients underwent radical therapy including radical pleurectomy / decortication and hyperthermic intrapleural lavage with povidone-iodine, adjuvant chemotherapy (platinum and pemetrexed combination chemotherapy) and prophylactic chest wall radiotherapy (21Gy in 3 fractions using orthovoltage radiation) [14]. Twenty-eight patients underwent palliative therapy including a videothoracoscopic procedure for talc pleurodesis or insertion of a pleurX catheter, usually followed by prophylactic radiotherapy on port sites (as above) and chemotherapy (as above).

Whilst ^{18}F-FDG PET/CT scans were performed for clinical staging in this cohort, the volume and intensity of active disease as measured by the PET parameters was not used for decisions between palliative or curative management options. In 4 cases it was not possible to measure SUVpeak as the required volume of tumour was too low or of a shape that could not accommodate a 1 cm^3 sphere and additionally in 2 of these cases SUVmean could not be calculated as it was not possible to confidently define the tumour edge for ROI definition.

No statistically significant differences in PET parameters were found between the epithelioid and non-epithelioid histological subtypes (Table 2).

Median follow up was for 12.7 months (1.9 - 60.9) and median OS was 14.1 months (1.9 - 54.9). Results of univariable and multivariable Cox regression analysis, used to examine the effects of PET parameters and other variables on overall survival outcomes, are shown in table 3. When examined individually, histological group, TLG and MTV were significantly associated with survival times ($p = 0.013$, 0.024 and 0.038, respectively). The other variables including age, sex, stage, SUVmean and SUVpeak were not significantly associated with patient survival

although SUVmax was borderline (p = 0.051). Epithelioid patients had a lower risk of death, with the risk of death at any time less than half that of non-epithelioid patients. The second stage in the analyses examined the joint association between the factors and survival times in a multivariable analysis. Before this analysis was performed variance inflation factors were calculated to assess collinearity between variables. These suggested that MTV and TLG were collinear and only TLG was subsequently included in the multivariable analysis. Additionally SUV max and SUVpeak were also found to be collinear and as SUVpeak was not significant in the univariable analysis it was omitted from the multivariable analyses. A backwards selection procedure was used to retain only variables showing some association with survival (histology and TLG). The final model is summarised in table 3. Of the variables considered for the multivariable analyses, there was some evidence that both histological group and TLG were associated with patient survival, although the results for both variables were only of borderline statistical significance (p = 0.060 and 0.058, respectively). As in the univariable analyses, patients in the epithelioid group had a lower risk of death, whilst the risk was higher in patients with higher TLG values. By Kaplan-Meier analysis of the factors that were significant in univariable analysis (histology, SUVmax, MTV and TLG), OS was lower in patients with non-epithelioid histology (median 8.3 vs 22.0 months, p = 0.01), high SUVmax > 6.3 (median 11.1 vs 46.6 months, p = 0.004), MTV > 755 ml (6.4 vs 14.4 months, p = 0.001) and TLG > 2914 ml (6.4 vs 18.1 months, p = 0.0002) (Fig. 1).

DISCUSSION

In a large series of patients with MPM we have shown that parameters derived from pre-treatment ^{18}F-FDG PET/CT scans that relate to the volume of metabolically active disease

(MTV) and both the volume and activity of disease (TLG = MTV x SUVmean), are associated with OS on univariable analysis whilst SUVmax was of borderline significance (p = 0.051). Relationships are stronger between OS and PET parameters that take into account the volume of metabolically active tumour (MTV) or both tumour activity and volume (TLG), than those that measure uptake only (SUVmax, SUVmean and SUVpeak). On multivariable analysis histology and TLG showed an association with OS, although both were of borderline statistical significance (p = 0.060 and 0.058, respectively). On Kaplan-Meier analysis of the factors showing significance in the univariable analysis, a difference in survival was seen between subjects with epithelioid and non-epithelioid histology, low and high values of SUVmax, MTV and TLG suggesting these variables could be further evaluated for stratifying patients. A relationship between ^{18}F-FDG uptake and prognosis is not unexpected in MPM as uptake of ^{18}F-FDG has previously been shown to be associated with Glut-1 and hexokinase 1 expression as well as factors related to hypoxia, angiogenesis, proliferation, cell cycle regulation and the mTOR signaling pathway; factors that are known to be associated with more aggressive behavior [15].

Although some previous studies have shown relationships between survival and SUVs in patients with MPM [6,7,16], this has not been confirmed in all [17,18]. There has been more recent interest in using prognostic PET parameters that also take metabolically active tumour volume into account, such as MTV and TLG (also referred to as total glycolytic volume or TGV) [18]. A longitudinal change in TLG (TGV) after chemotherapy has also been shown to predict response after one cycle and is associated with survival [19].

The use of parameters that take both tumour activity and tumour volume into account in determining prognosis is intuitive, as both tumour activity and total tumour burden are

related to outcome in many tumours. TLG has been used in previous analyses of non-mesothelioma tumours as a global measure of all sites of tumour for response assessment [20,21] and it has been recommended that TLG data is acquired in trials for secondary analysis [11]. In MPM, changes in SUVmax and TLG have been reported to be inferior to morphological response assessment to chemotherapy [22] and in another study MTV and TLG treatment response changes were predictive of survival [23]. A further study found MTV and TLG to be predictive for recurrence after surgery or progression following chemotherapy [24].

Different histological subtypes have been reported as being related to OS and in particular sarcomatoid histology is associated with a poor prognosis [18]. On ^{18}F-FDG PET analysis, an association has been reported between TGV and OS in a univariable analysis of 89 patients but only in non-sarcomatoid (n = 82) patients on multivariable analysis [18]. However, sarcomatoid histology is relatively rare and it was suggested that these patients should be considered as a different group for stratification. Variation in SUVmax between subtypes of epithelioid tumours has been described with more pleomorphic subtypes being over represented in a group with high SUVmax [25]. A positive correlation with mitotic count was also reported.

Patients with MPM are frequently treated with pleurodesis. This procedure causes an inflammatory reaction in the pleura that can be associated with intense ^{18}F-FDG activity [26] and this is a potential limitation for analysing MPM tumour activity on PET scans. Despite this, MTV (TGV) has been reported to retain predictive power for survival in a subgroup analysis of patients with previous talc pleurodesis [18]. In our study, only patients without any form of prior treatment were included to exclude any confounding effects on ^{18}F-FDG accumulation and so we were unable to assess the effects of previous pleurodesis in our

cohort. This study is also limited by its retrospective nature and the patient group included those selected for radical and palliative therapy options. Whilst therapeutic strategies for mesothelioma may have changed during the period that ^{18}F-FDG PET/CT scans were included in this study, it is recognised that there has been little impact in prognosis of MPM worldwide [2,3] and it is therefore unlikely that significant changes in prognosis and OS will have evolved over the study period to bias our results. Whilst there were sufficient patients with epithelioid histology for subgroup analysis, other histological subtypes had too few patients for meaningful comparison and histological data was missing in 9 cases.

CONCLUSION

^{18}F-FDG PET/CT parameters that take into account functional volume (MTV, TLG) show significant associations with survival in patients with MPM before adjusting for histological subtype. Prospective evaluation is required but PET parameters show promise as possible methods to stratify patients in clinical trials.

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Conflict of Interest statement: The authors declare that they have no conflict of interest.

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TABLES

Table 1. Patient demographic and clinical characteristics.

Patient Characteristics	Number (%)
Age mean and [range]	64.8 years (45-79)
Gender Male Female	 51 (85%) 9 (15%)
Histological subtype Epithelioid Sarcomatoid Mixed Desmoplastic Unknown	 31 (52%) 5 (8%) 13 (22%) 2 (3%) 9 (15%)
Overall tumour stage (AJCC) 1 2 3 4	 9 (15%) [T1N0M0, n=9] 13 (22%) [T2N0M0, n=13] 27 (45%) [T2N1M0, n=3, T2N2M0, n=8, T3N0M0, n=12, T3N1M0, n=2, T3N2M0, n=2] 11 (7%) [T2N3M0, n=2, T4N0M0, n=3, T4N2M0, n=3, T4N2M1, n=1, T4N3M1, n=2]
Therapy Radical Palliative	 32 (53%) 28 (47%)

(AJCC - American Joint Committee on Cancer 7th edition [27])

Table 2. PET parameters in histological subtypes

Parameter	Mean epithelioid	Mean non-epithelioid	S.D.	P value
SUVmax	11.5	11.6	6.6 (4.9)	0.69
SUVmean	4.5	4.5	1.9 (1.7)	0.95
SUVpeak	10.1	9.4	5.3 (3.9)	0.32
TLG (ml)	2392	2704	3039 (3061)	0.97
MTV (ml)	436	551	424 (582)	0.90

S.D. standard deviation. Non-epithelioid S.D. in parentheses.

Table 3: Univariable and multivariable analyses

Variable	Category	Univariable analysis		Multivariable analysis	
		Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age (**)	-	0.96 (0.64, 1.44)	0.84		
Sex	Male	1	0.22		
	Female	0.56 (0.22, 1.41)			
Histological group	Non-Epithelioid	1	0.013	1	0.060
	Epithelioid	0.43 (0.22, 0.84)		0.53 (0.28, 1.03)	
Stage	1	1	0.34		
	2	0.50 (0.18, 1.39)			
	3	0.98 (0.43, 2.23)			
	4	1.21 (0.46, 3.14)			
SUVmax (*)	-	1.26 (1.00, 1.58)	0.051		
SUVmean	-	1.11 (0.96, 1.28)	0.15		
SUVpeak (*)	-	1.26 (0.93, 1.69)	0.14		
TLG (†)	-	1.25 (1.03, 1.52)	0.024	1.25 (0.99, 1.51)	0.058
MTV (†)	-	1.27 (1.01, 1.58)	0.038		

The effects of variables on overall survival in univariable and multivariable analyses.

(*) Hazard ratios given for a 5-unit increase in explanatory variable

(**) Hazard ratios given for a 5-unit increase in explanatory variable

(†) Variable analysed on log scale

FIGURE LEGENDS

FIGURE 1. Kaplan-Meier plots showing differences in overall survival (OS) between patients with i) epithelioid and non-epithelioid histology, ii) SUVmax, iii) MTV and iv) TLG.